

Cutaneous Radiation Syndrome and Radiation-Induced Multi-Organ-Involvement

H. D. Dörr and V. Meineke



Bundeswehr Institute of Radiobiology

Cutaneous Radiation Syndrome and Radiation-Induced Multi-Organ-Involvement

Database SEARCH – Cutaneous Radiation
Syndrome

Combined Injuries – InstRadBioBw Studies (1977)

3D Skin Model – Model for Combined Injuries

Radiation-Induced Multi-Organ-Involvement

METREPOL Concept

Cutaneous Radiation Syndrome and Radiation-Induced Multi-Organ-Involvement

Database SEARCH – Cutaneous Radiation Syndrome

Combined Injuries – InstRadBioBw Studies (1977)

3D Skin Model – Model for Combined Injuries

Radiation-Induced Multi-Organ-Involvement

METREPOL Concept

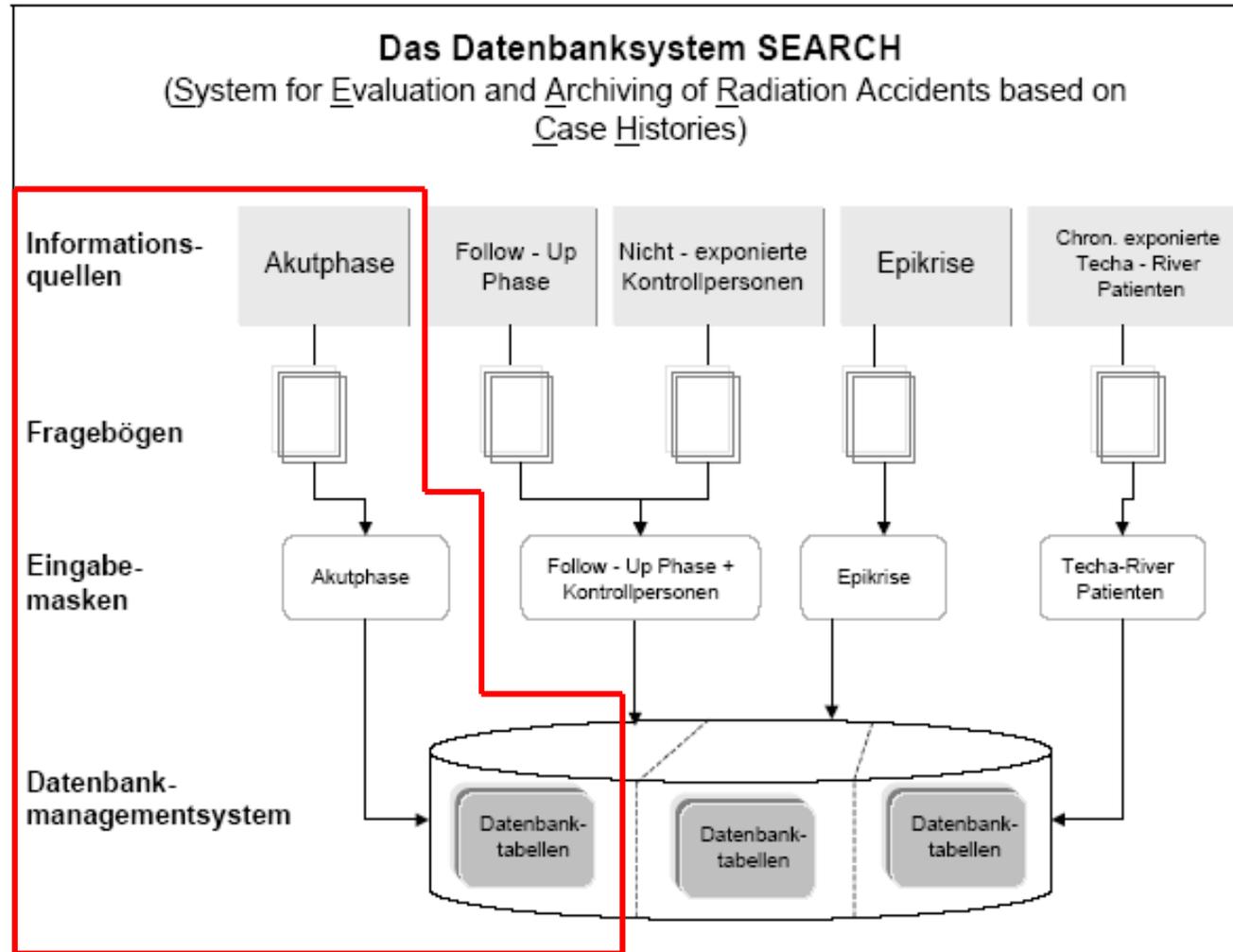
SEARCH

(System for Evaluation and Archiving of Radiation Accidents based on Case Histories)

The screenshot displays the DaWIT-45 software interface, which is used for searching and archiving radiation accident case histories. The interface is divided into several sections:

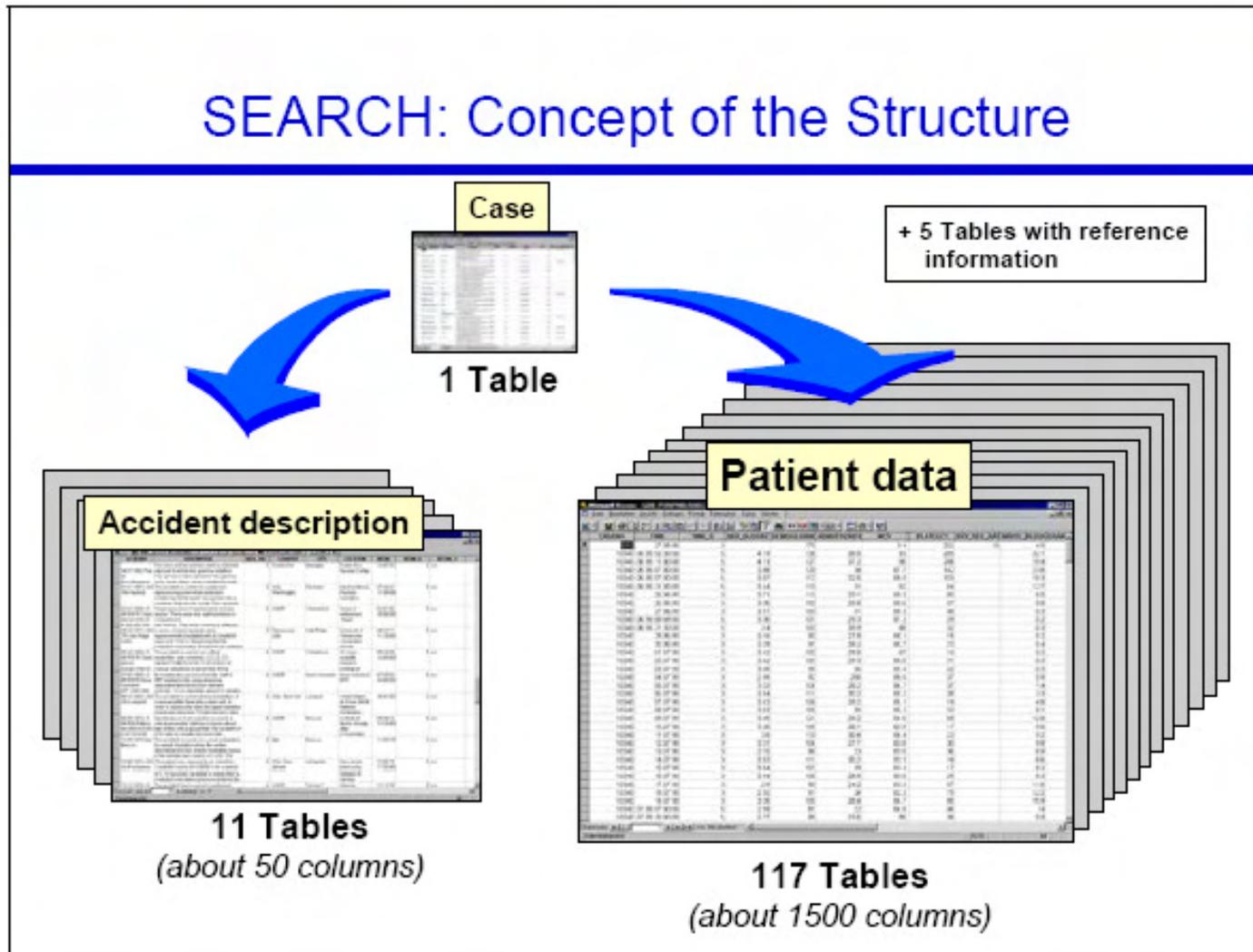
- Search Criteria:** Located at the top, it includes fields for Caseno (45), Accident (21.03.1962.Mexico.Mexico City), Family Name, Given Name, Gender (m), Day of Birth, Survival Status (death), and Day of Death (29.04.1962 00:00:00).
- Table of Contents:** A sidebar on the left lists various categories of patient information, including General Patient Info, Social, Habits, Living Situation, Education, Period Life, Occupation, and Survival Status.
- General Patient Info:** A central panel displaying detailed patient information, including Individual Accident Info, Bone Marrow - Haem. Syst., Skin, GIT, Pulmonary Function - Lunge, Urogenital, and Cardio - Card. Vasc.
- Laboratory Results:** A panel on the right showing four line graphs for Hemoglobin, Hematocrite, Bloodcell, and Granulocyte, plotted against Days (d). The Hemoglobin and Hematocrite graphs show a decrease over time, while the Bloodcell and Granulocyte graphs show an increase.
- Navigation and Analysis Tools:** A bottom panel with buttons for Blood Cells, Cyto Genetics, Endocrine, Immunology, Laboratory Examination, Diagnosis, Treatment, Transfusion, Transplantations, and References.

SEARCH



SEARCH

SEARCH: Concept of the Structure

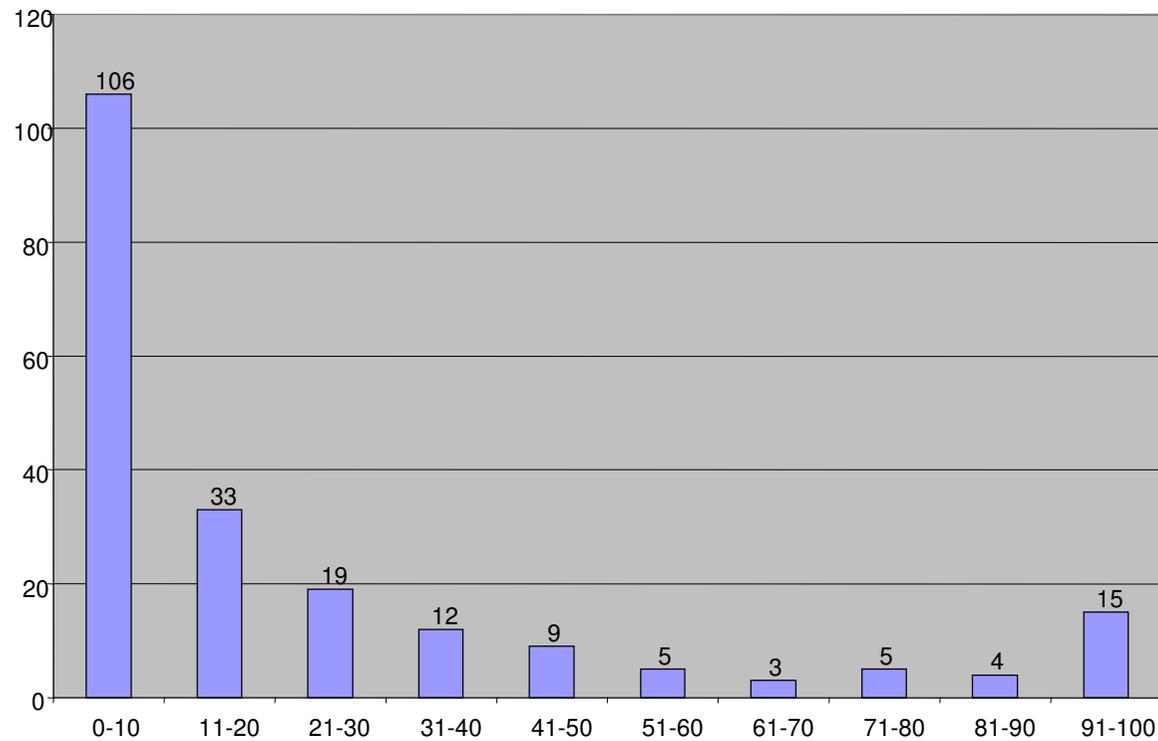


Aim of the analysis

Analysis of the clinical course of radiation induced skin reactions.

The importance of the clinical course and the degree of radiation induced skin reactions for the prognosis of the acute radiation syndrome.

Percentage of affected body surface in 206 patients



Betroffene KOF in %	Patientenzahl N	Prozent
0-10	106	50,24
11-20	33	15,64
21-30	19	9
31-40	12	5,69
41-50	9	4,27
51-60	5	2,37
61-70	3	1,42
71-80	5	2,37
81-90	4	1,9
91-100	15	7,11

Conclusions

The prognosis of the clinical course of the acute radiation syndrome strongly depends on the extension of affected skin surface.

Radiation induced skin reactions appear to be an independent prognostic parameter for patients with ARS.

Skin Reaction to Ionizing Radiation depends on Exposure Conditions

- Time: acute / chronic or intermittent irradiation
- Dose: high / low dose irradiation
- Types of radiation: RBE (alpha / beta / gamma/ neutron radiation)

⇒ Clinical endpoint of early and late skin reactions

Role of Skin in Radiation-Induced Multi-Organ Failure

- Diagnostic parameter
- Critical organ
- Trigger factor (e.g. immune reactions)
- Determination of the point of no return?
- Successful treatment of skin complications might help to avoid multi-organ failure

Cutaneous Radiation Syndrome and Radiation-Induced Multi-Organ-Involvement

Database SEARCH – Cutaneous Radiation
Syndrome

Combined Injuries – InstRadBioBw Studies (1977)

3D Skin Model – Model for Combined Injuries

Radiation-Induced Multi-Organ-Involvement

METREPOL Concept

Studies on Combined Injuries

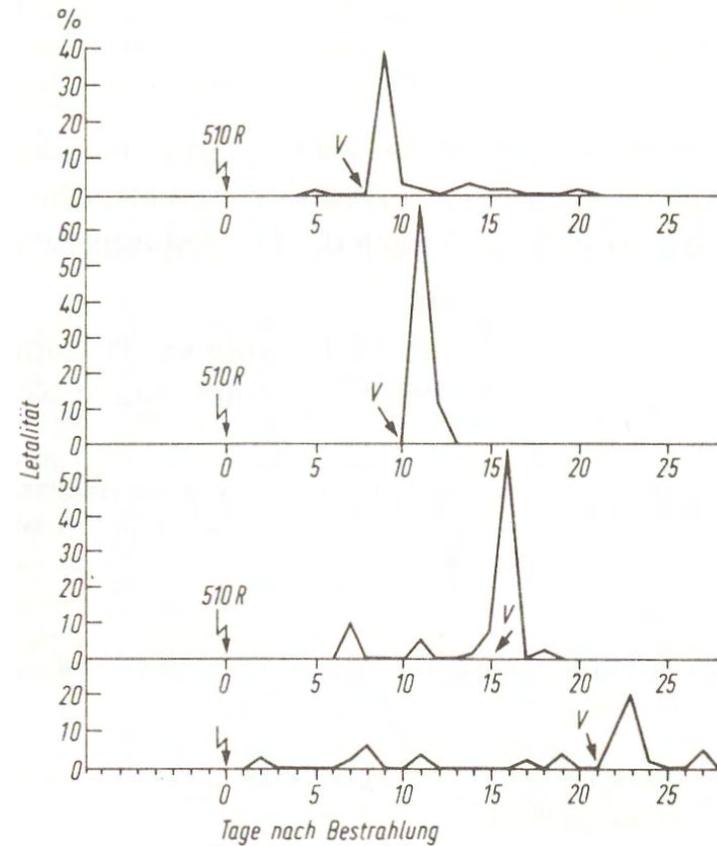
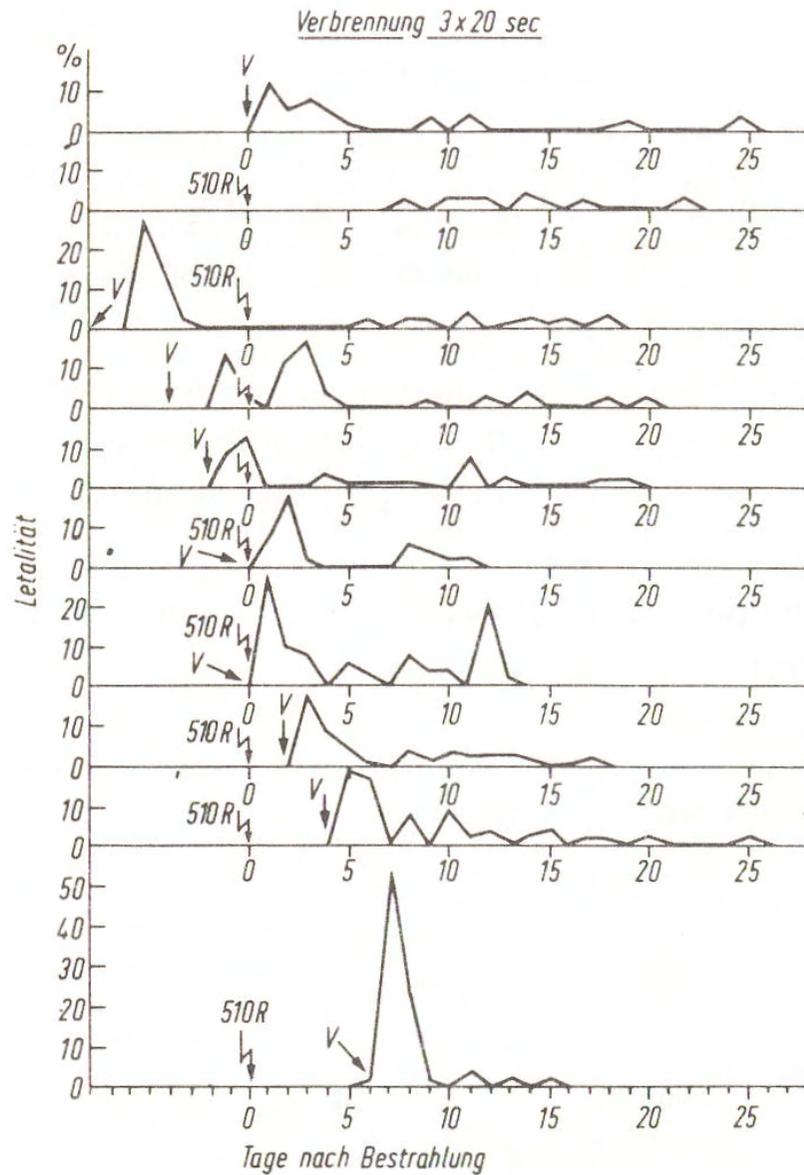
**Studies performed by
Colonel Prof. O. Messerschmidt et al.
at Bundeswehr Institute of Radiobiology**

Animal model (mice)

Studies on Combined Injuries

**radiation exposure
and
thermal burns**

Lethality of Combined Injuries

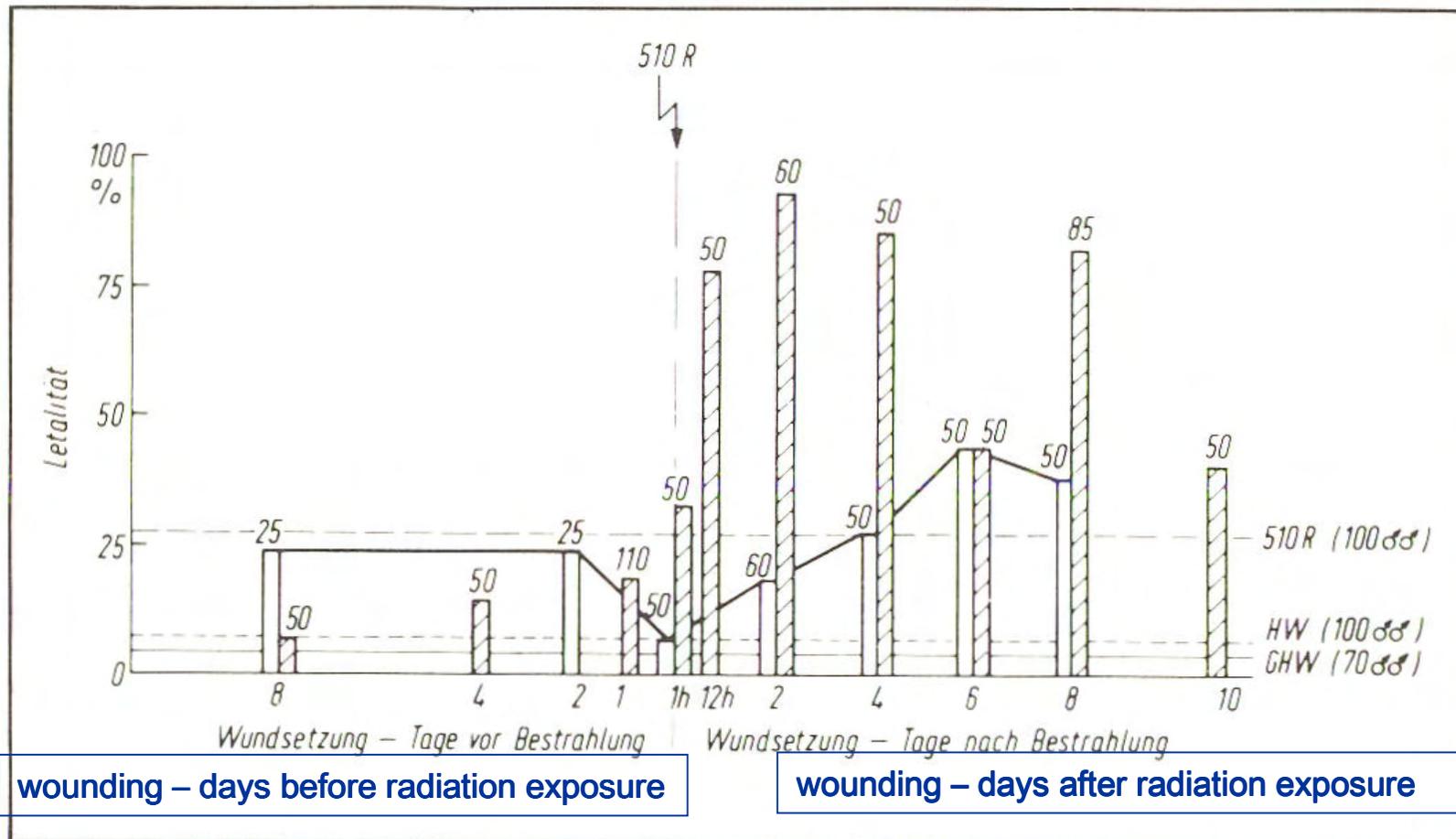


O. Messerschmidt et al. 1977

Studies on Combined Injuries

**radiation exposure
and
Skin Wounds**

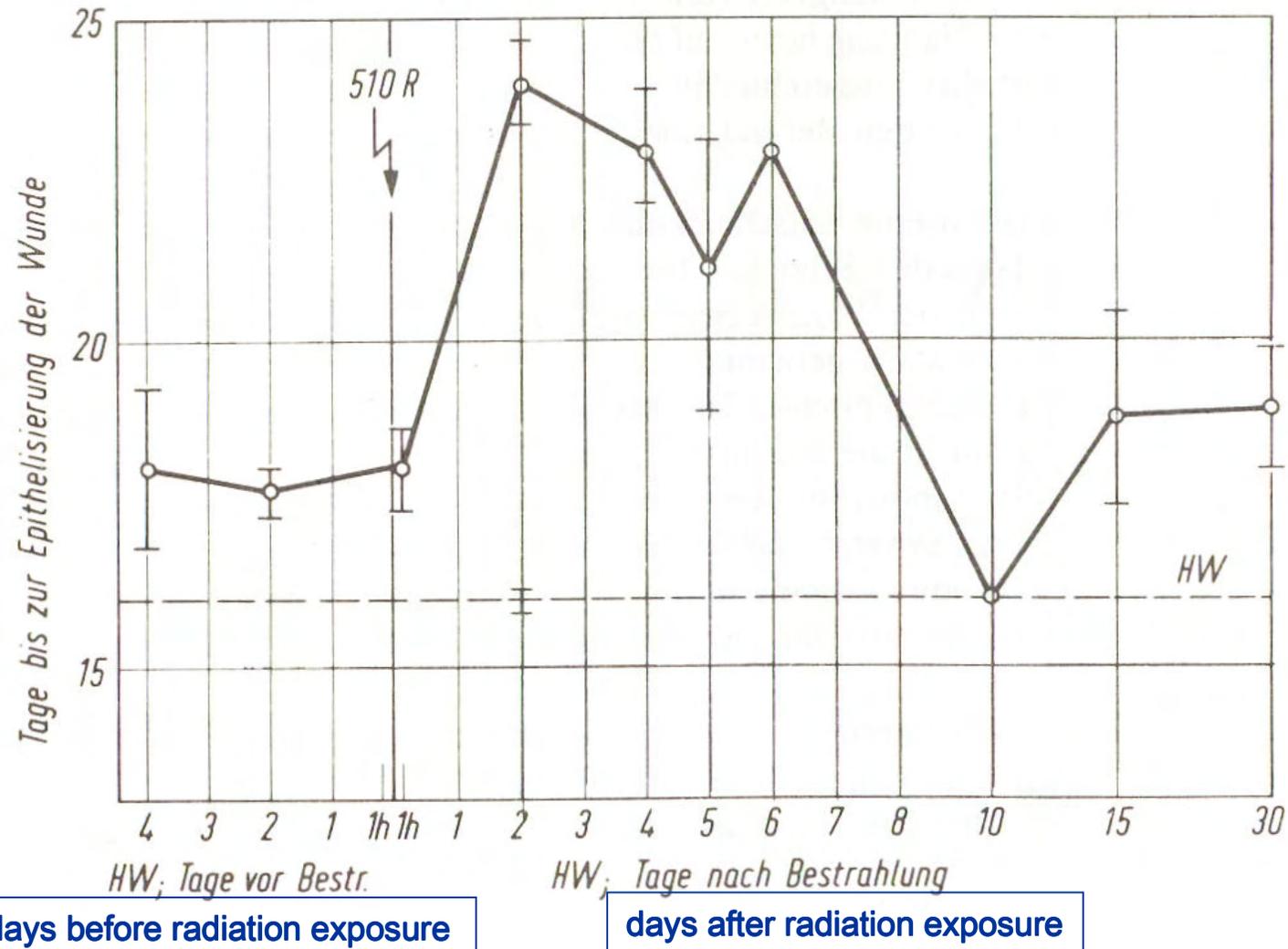
Lethality of Combined Injuries



wounding – days before radiation exposure

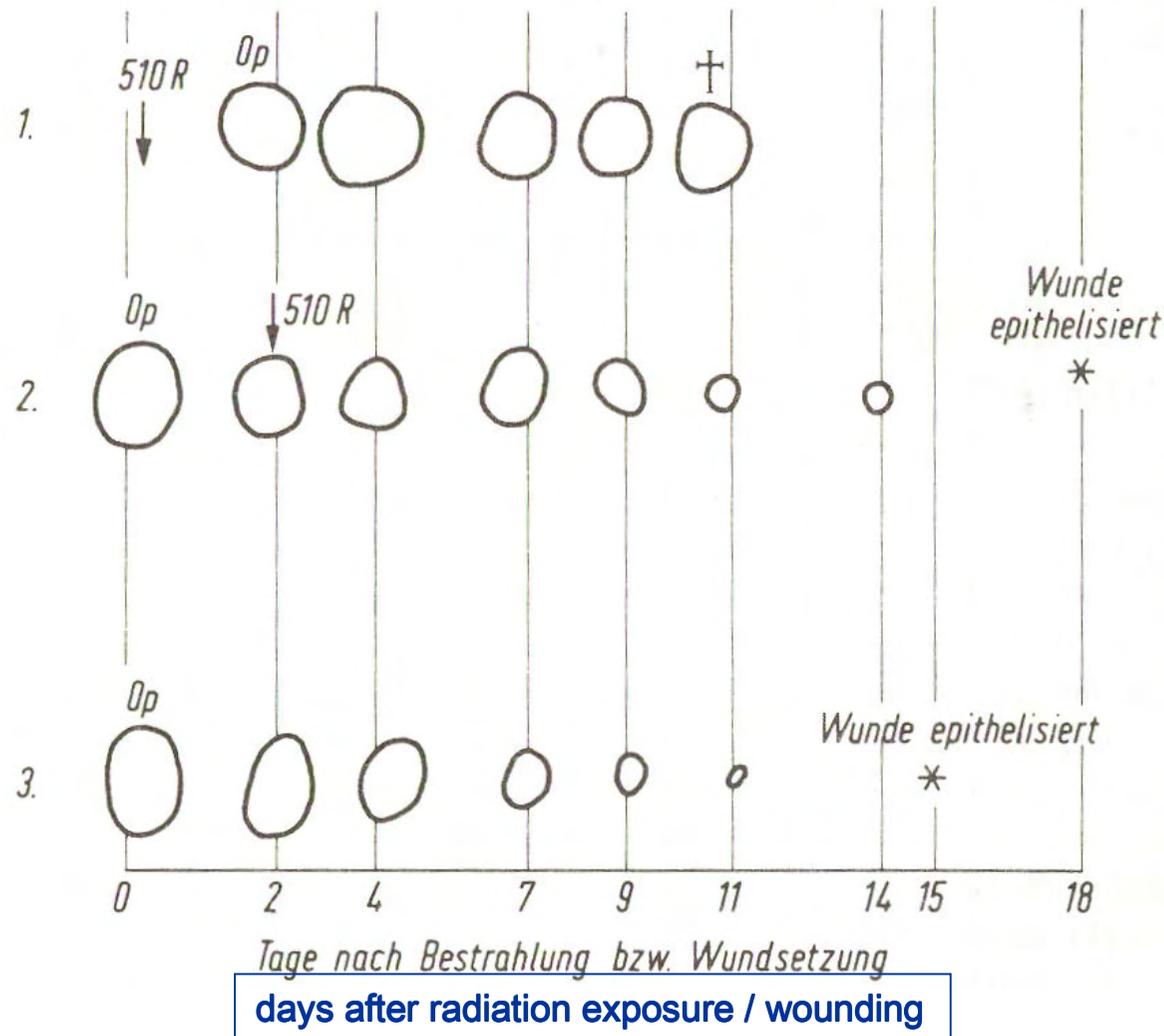
wounding – days after radiation exposure

Wound Healing after Radiation Exposure



O. Messerschmidt et al. 1977

Wound Healing after Radiation Exposure



O. Messerschmidt et al. 1977

Cutaneous Radiation Syndrome and Radiation-Induced Multi-Organ-Involvement

Database SEARCH – Cutaneous Radiation
Syndrome

Combined Injuries – InstRadBioBw Studies (1977)

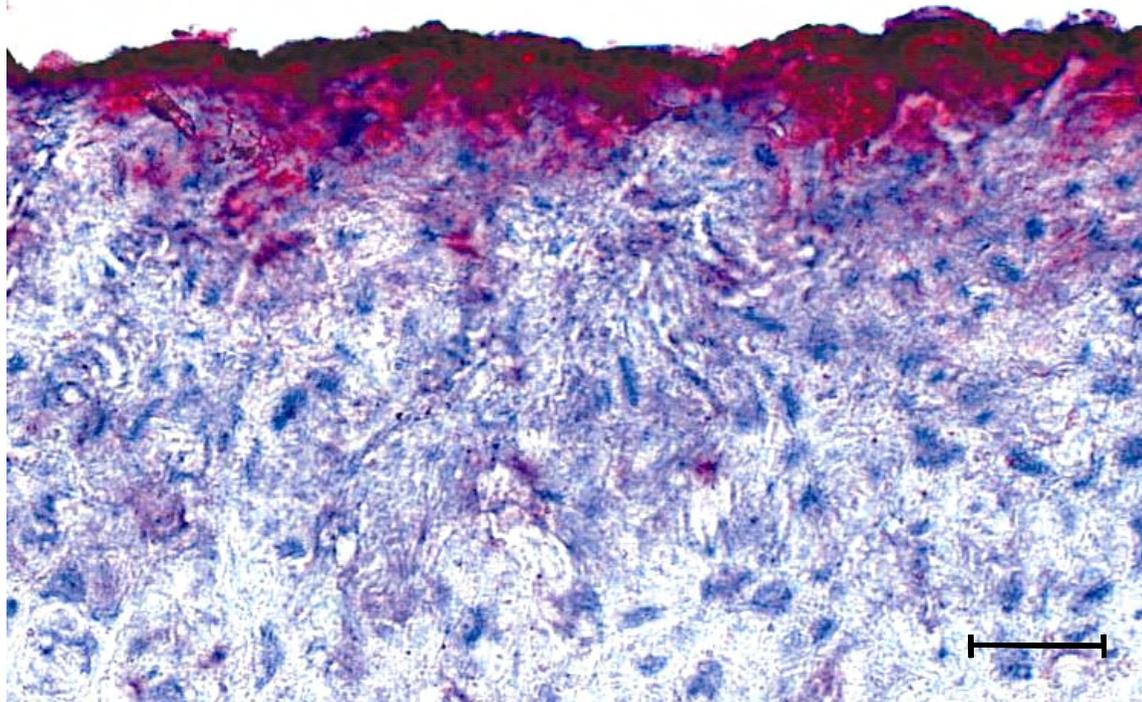
3D Skin Model – Model for Combined Injuries

Radiation-Induced Multi-Organ-Involvement

METREPOL Concept

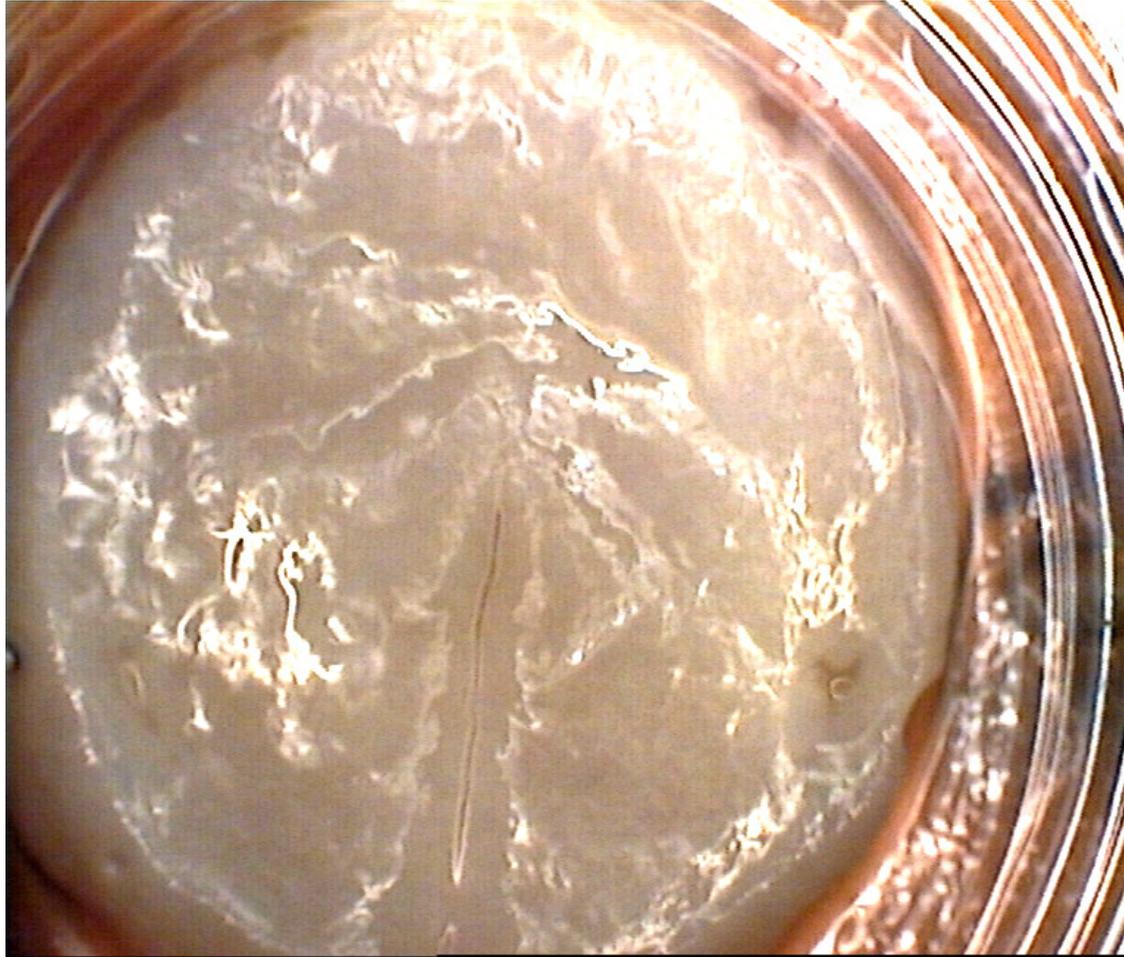
3D Skin Model

**model for cutaneous radiation
syndrome and combined injuries**

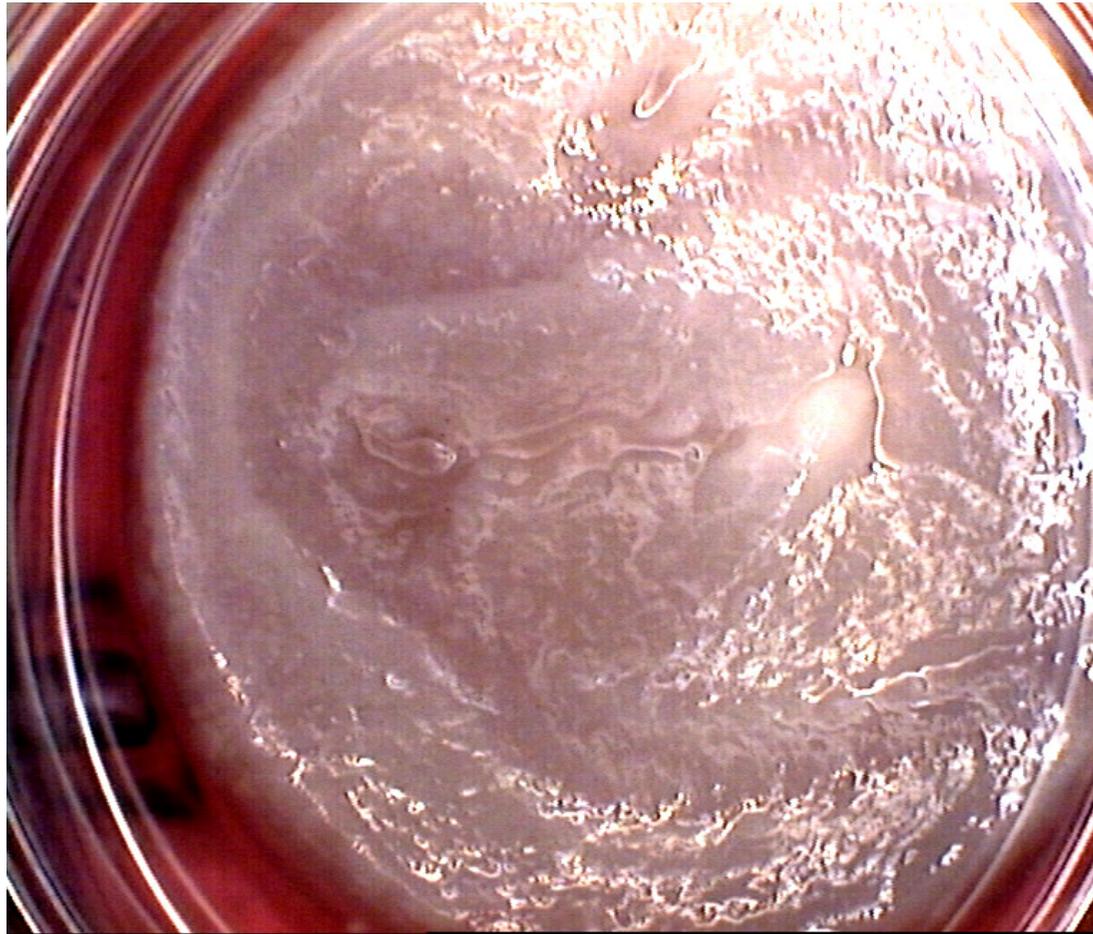


Skin Model (6 weeks old), 48 h p.r. (5 Gy). The immunohistochemical staining of β 1-Integrins (APAAP) shows more intensive staining in the upper region (Epidermis (++))
Meineke et al. , Strahlenther Onkol. 2004;180:102-8.

3D Skin Model “wounded”



3D Skin Model



Cutaneous Radiation Syndrome and Radiation-Induced Multi-Organ-Involvement

Database SEARCH – Cutaneous Radiation
Syndrome

Combined Injuries – InstRadBioBw Studies (1977)

3D Skin Model – Model for Combined Injuries

Radiation-Induced Multi-Organ-Involvement

METREPOL Concept

Radiation-Induced Multi-Organ Involvement and Failure



Acute Radiation Syndrome:

Pathophysiological Concepts

- Classical View: The "acute radiation syndrome" is the consequence of the exposure of the whole organism with ionising radiation (gamma-, x-rays, neutrons etc.). It results in characteristic perturbations especially of hematopoietic, gastrointestinal and central-nervous functional properties but also the skin.
- Recent View: The "radiation syndrome" evolves in a regular and reproducible manner as a function of time after short-term as well as protracted or chronic exposure of the whole organism with the consequences of affecting all cells, cell systems and organ systems (multiorgan involvement), depending on their cell turnover, their functional potentials and system interactions. Multiorgan failure develops if these adaptive potentials are exceeded.

Multiorgan – Involvement as an Pathogenetic Principle - Methods used for the Study -

- The Ulm Database SEARCH (System for Evaluation and Archiving of Radiation Accident based on Case Histories) contains >800 case reports of 81 radiation accidents reported from 19 countries that occurred between 1945 and 2001.
- A systematic analysis of 110 case histories from patients with a severe form of an acute radiation syndrome was used to assess the type, extent and significance of multi-organ involvement.
- On the basis of „Severity of Effect Codes“ developed for the METREPOL-concept of radiation accident medical management using the pattern of blood cell changes as indicators of damage to the stem-cell pool, 45 patients were assigned to the code „H4“ (irreversible damage) and hence „RC 4“, and 65 patients to H 3 (reversible damage) and hence „RC 3“

Morbidity and Mortality relating to Organinvolvement and –Failure within Acute Radiation Syndrome at Grading RC 4 (Death within < 60 Days, n = 45)

survivaltime [days]	n (total)	hemopoetic- system	skin	GIT	CNS	kidney	liver	respiratory sytem	cardiovasc.- system
0-10	8	8	7	8	8	5	2	5	7
11-20	15	15	15	15	15	11	7	10	5
21-30	12	12	12	12	12	9	8	8	5
31-40	6	6	6	6	6	4	5	6	0
Σ	45	45	43	45	45	32	25	32	20

T.M. Fliedner, H.D. Dörr and V. Meineke, British Journal of Radiology (2005) Supplement 27

Morbidity and Mortality relating to Organinvolvement and –Failure within Acute Radiation Syndrome at Grading RC 3 (Within 90 Days after Radiation-Exposure)

n (total)	hemopoetic- system	skin	GIT	CNS	kidney	liver	respiratory sytem	cardiovasc.- system
65	65	58	61	50	9	18	5	14

Indicators of Organ-Involvement:

- hemopoetic system: aberration of peripheral blood cell count
- skin: epilation, erythema, ulceration
- gastrointestinal tract: mucositis, vomiting, diarrhea
- central nervous system: headache, fatigue, dizziness, coma
- kidney: biochemical parameters (crea., urea), anuria
- liver: biochemical parameters (ALT, AST, GGT, bili.), jaundice
- respiratory system: pneumonia, respiratory failure
- cardiovascular system: hypotension, heart failure

Cutaneous Radiation Syndrome and Radiation-Induced Multi-Organ-Involvement

Database SEARCH – Cutaneous Radiation
Syndrome

Combined Injuries – InstRadBioBw Studies (1977)

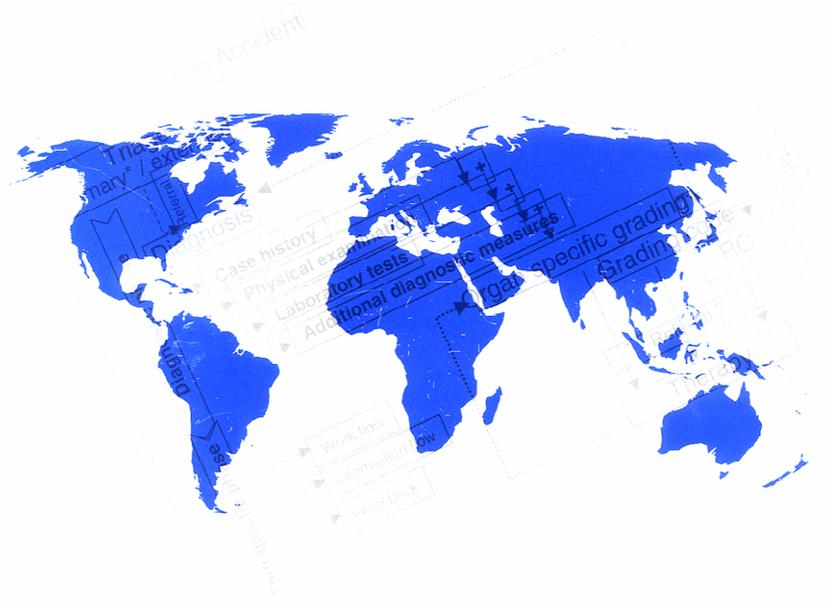
3D Skin Model – Model for Combined Injuries

Radiation-Induced Multi-Organ-Involvement

METREPOL Concept

MEDICAL MANAGEMENT OF RADIATION ACCIDENTS

Edited by T M Fliedner, I Friesecke and K Beyrer



MANUAL ON THE ACUTE RADIATION SYNDROME

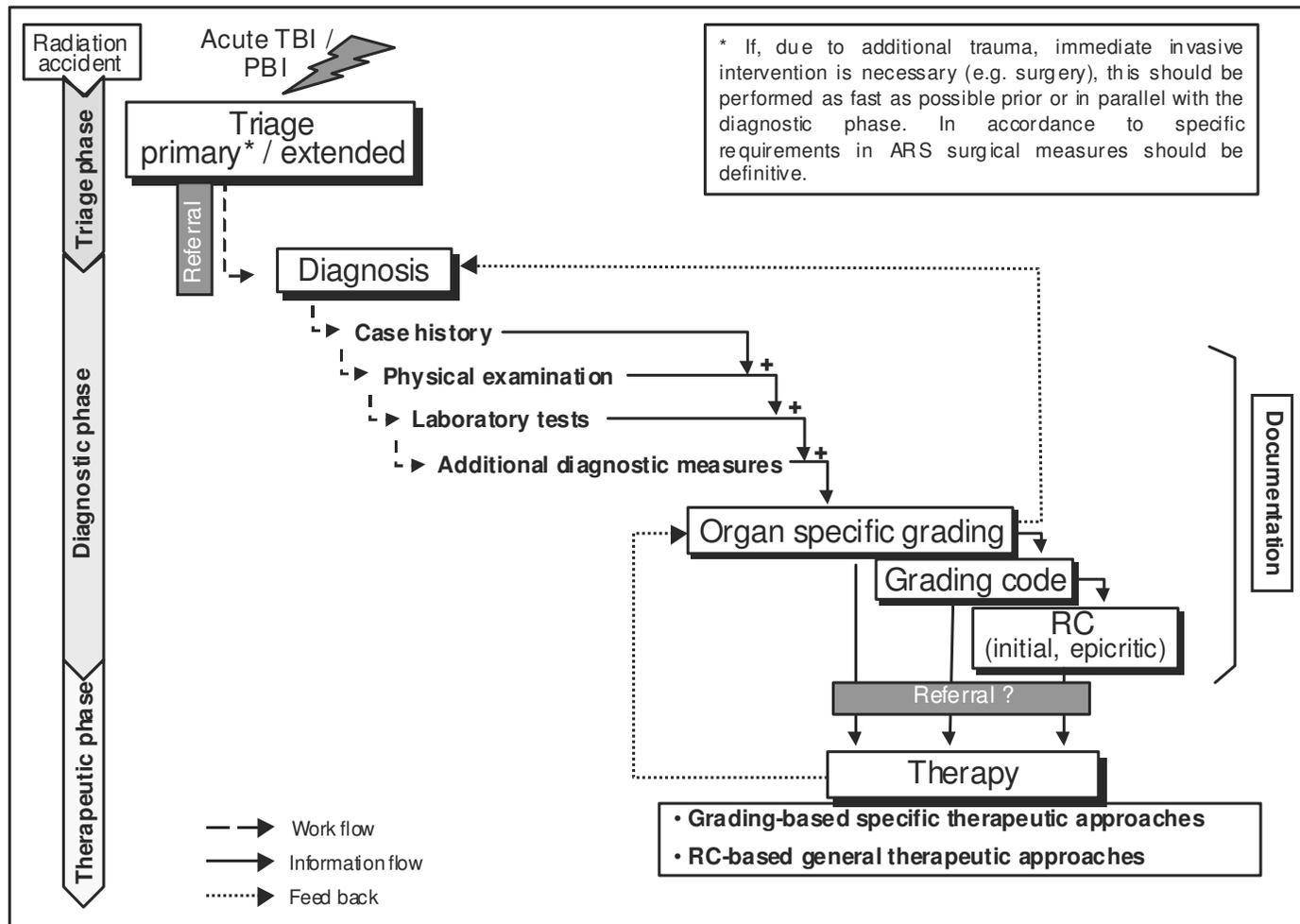
BIR Published by The British Institute of Radiology

EU-METREPOL

Concept for a Professional Medical Radiation Accident Management

- An EU-Concerted Action METREPOL (Medical Treatment Protocols for Radiation Accident Victims) resulted in an entirely new approach to manage accident victims on the basis of indicators of effect and repair considering multiorgan involvement and potential treatment options.
- Publication: T. M. Fliedner, I. Friesecke, K. Beyrer (Edit.): Medical Management of Radiation Accidents: Manual on the Acute Radiation Syndrome
British Institute of Radiology, London, 2001

Diagnostic Approach to Evaluate the Radiation Effects as a Function of Time to Develop Therapeutic Strategies



Early Clinical Signs and Symptoms of Radiation Exposure

Table 1. Symptoms of special relevance in assessing the extent of radiation induced damage (in alphabetical order)

Abdominal cramps/pain	Erythema	Nausea
Anorexia	Fatigue syndrome	Neurological deficits
Blistering	Fever	Onycholysis
Blood loss	Granulocyte changes	Sensation/itching
Cognitive deficits	Hair loss	Swelling and oedema
Desquamation	Headache	Thrombocyte changes
Diarrhoea (characterised by frequency, consistency, mucosal loss and bleeding)	Hypotension	Ulcer/necrosis
	Infection	Vomiting
	Lymphocyte changes	

Grading and Response Categories

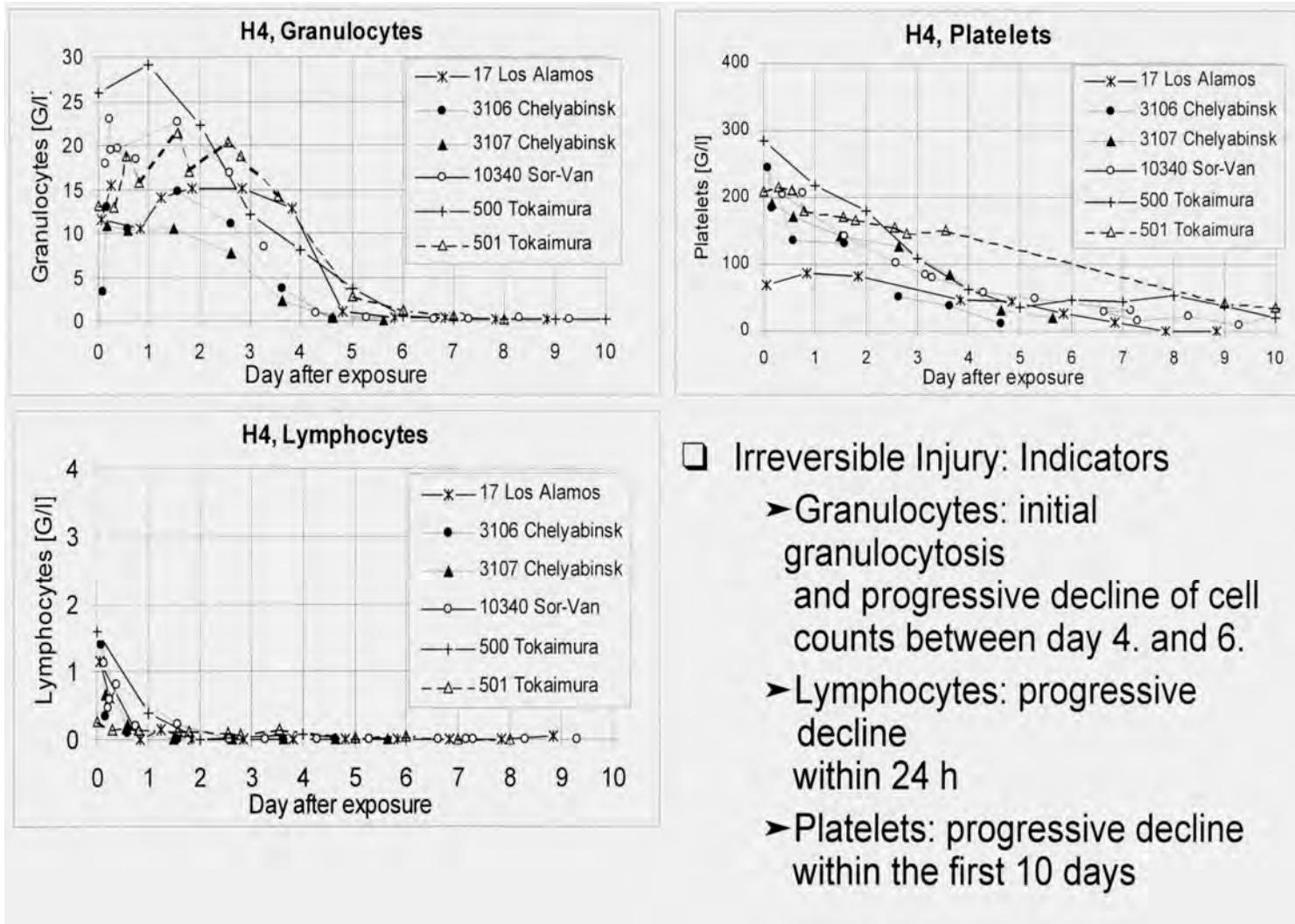
Table 2. Overall prognostic aspects of the ARS on the basis of the organ specific grading

Organ system	Grading and severity of damage			
	1: mild damage	2: moderate damage	3: severe damage	4: serious/fatal damage
N	Recovery certain	Recovery with possible deficit	Recovery with severe deficit	Recovery most unlikely
H	Autologous recovery certain	Autologous recovery likely	Autologous recovery possible	Autologous recovery most unlikely
C	Recovery certain	Recovery without deficit likely	Recovery with deficit likely	Recovery most unlikely or with serious deficit
G	Recovery certain	Recovery with possible deficit	Recovery may be possible	Recovery most unlikely

Grading of the hematopoietic system

Grading	Extent of impairment	Prognosis
H1	Mild damage	Autologous recovery certain without critical phase
H2	Moderate damage	Autologous recovery certain with low risk critical phase
H3	Severe damage	Autologous recovery certain with high risk critical phase
H4	Fatal damage	Autologous recovery most unlikely

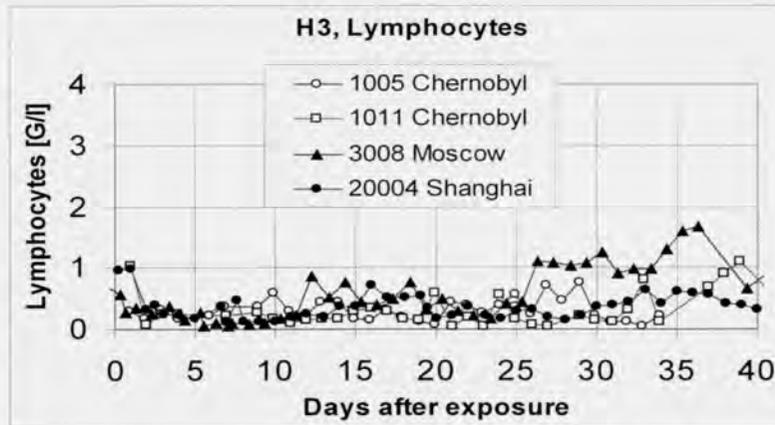
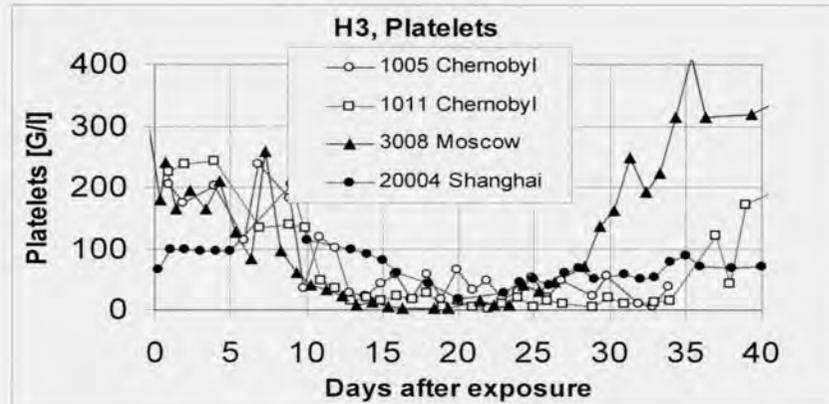
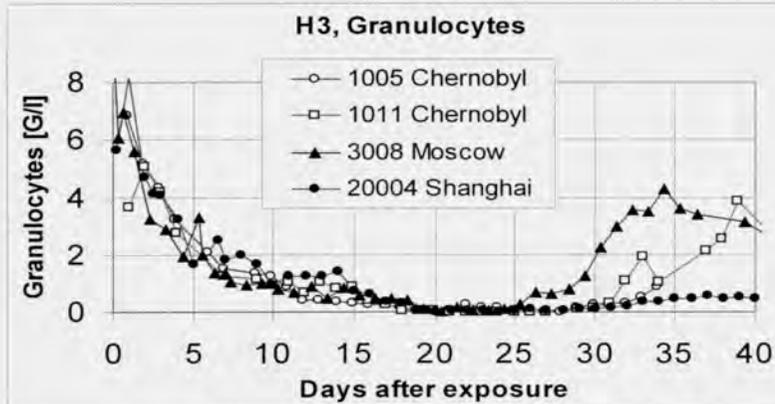
Severity of effect code“ H4 (irreversible damage) of hemo- poiesis as a common denominator for all patients in RC 4.



□ Irreversible Injury: Indicators

- Granulocytes: initial granulocytosis and progressive decline of cell counts between day 4. and 6.
- Lymphocytes: progressive decline within 24 h
- Platelets: progressive decline within the first 10 days

Severity of effect code“ H3 (reversible injury) of hematopoiesis as a common denominator for 65 patients:



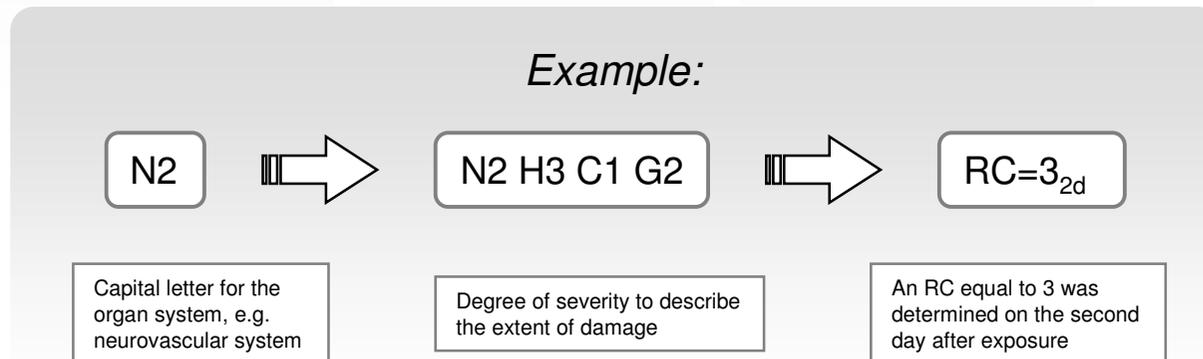
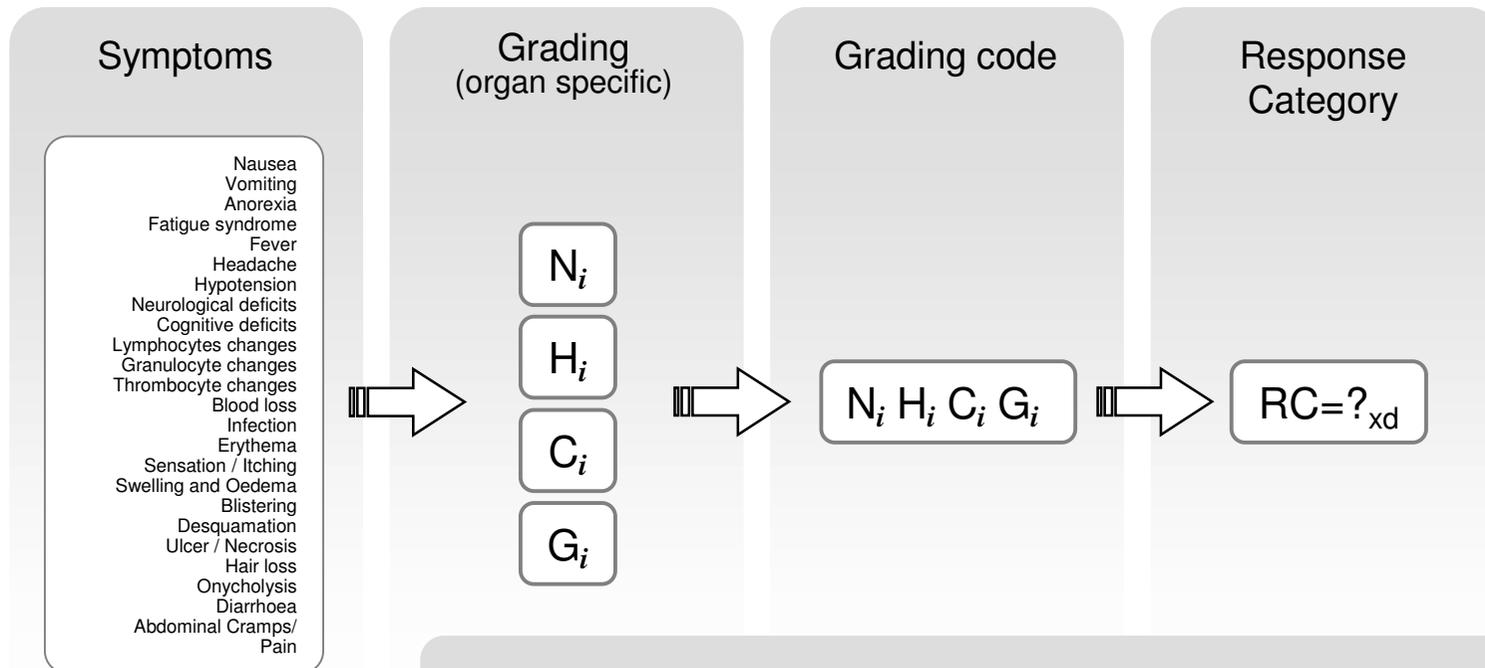
- Reversible Injury: Indicators
- Granulocytes: moderate granulocytosis, decline between day 4. and 10., abortive recovery followed by nadir: days 20.-30.
 - Lymphocytes: decline to nadir-levels within 2 days, thereafter slow recovery
 - Platelets: initial 10-day-shoulder followed by decline towards day 20., nadir: days 20.-30.

Organ-Specific Checklists

Symptom	Degree 1	Degree 2	Degree 3	Degree 4			
G							
Diarrhoea							
Frequency	2 – 4 stools / d	5 – 8 stools / d	> 8 stools / d	refractory diarrhoea			
Consistency							
Mucosal Loss/ d							
H							
Bleeding / d	Granulocytes (4-9 x10 ⁹ /l)	> 2 x10 ⁹ /l	1-2 x10 ⁹ /l	0,5-1 x10 ⁹ /l	< 0.5 x10 ⁹ /l		
Abdominal Cramps/ Pain	Infection						
C							
	Erythema	minimal and transient	moderate isolated patches <	marked, isolated patches or	severe isolated patches or		
	Thrombocytes (140-400 x10 ⁹ /l)						
	Blood loss						
N							
	Sensation/Itching	Nausea	mild	tolerable	intense	excruciating	
		Vomiting	occasional 1 / d	intermittent 2 – 5 / d	persistent 6 – 10 / d	refractory > 10 / d or parenteral nutrition	
	Swelling and Oedema						
	Lymphocytes (1.5-4 x10 ⁹ /l)	Blistering	Anorexia	able to eat, reasonable intake	significantly decreased intake but able to eat	no significant intake	parenteral nutrition
		Desquamation					
		Ulcer / Necrosis	Fatigue Syndrome	able to work or perform normal activity	interferes with work or normal activity	needs some assistance for self-care	prevents daily activity
		Hair loss	Fever without infection	< 38°C	38 – 40°C	> 40°C for less than 24 h	> 40°C for more than 24 h or accompanied with hypotension
		Pigmentation (Hyper/Hypo)	Headache	minimal	tolerable	intense	excruciating
		Onycholysis	Hypotension	∅	∅	transient	persistent
			Neurologic deficit	barely detectable neurologic deficit , able to perform normal activity	easily detectable neurologic deficit, no significant interference with normal activity	prominent neurologic deficit, significant interference with normal activity	life threatening neurologic signs, loss of consciousness
			Cognitive functions	minor loss of memory, reason and/or judgement	moderate loss of memory, reason and/or judgement	major intellectual impairment	complete memory loss and/or incapable of rational thoughts

N = Neurovascular System
H = Hematopoietic System
C = Cutaneous System
G = Gastrointestinal System

Assessment of Severity and Complexity of Radiation Effects: Establishment of a "Grading Code" of Organ Involvement and of a "Response Category" as a Function of Time



N = Neurovascular System
H = Haematopoietic System
C = Cutaneous System
G = Gastrointestinal System
i = Degree of severity 1-4
xd = Time point (*x*) at which RC was established; measured in days (*d*) after begin of exposure.

Principles to Cope Therapeutically with Consequences of Whole Body Radiation Exposure During the “Acute Phase”

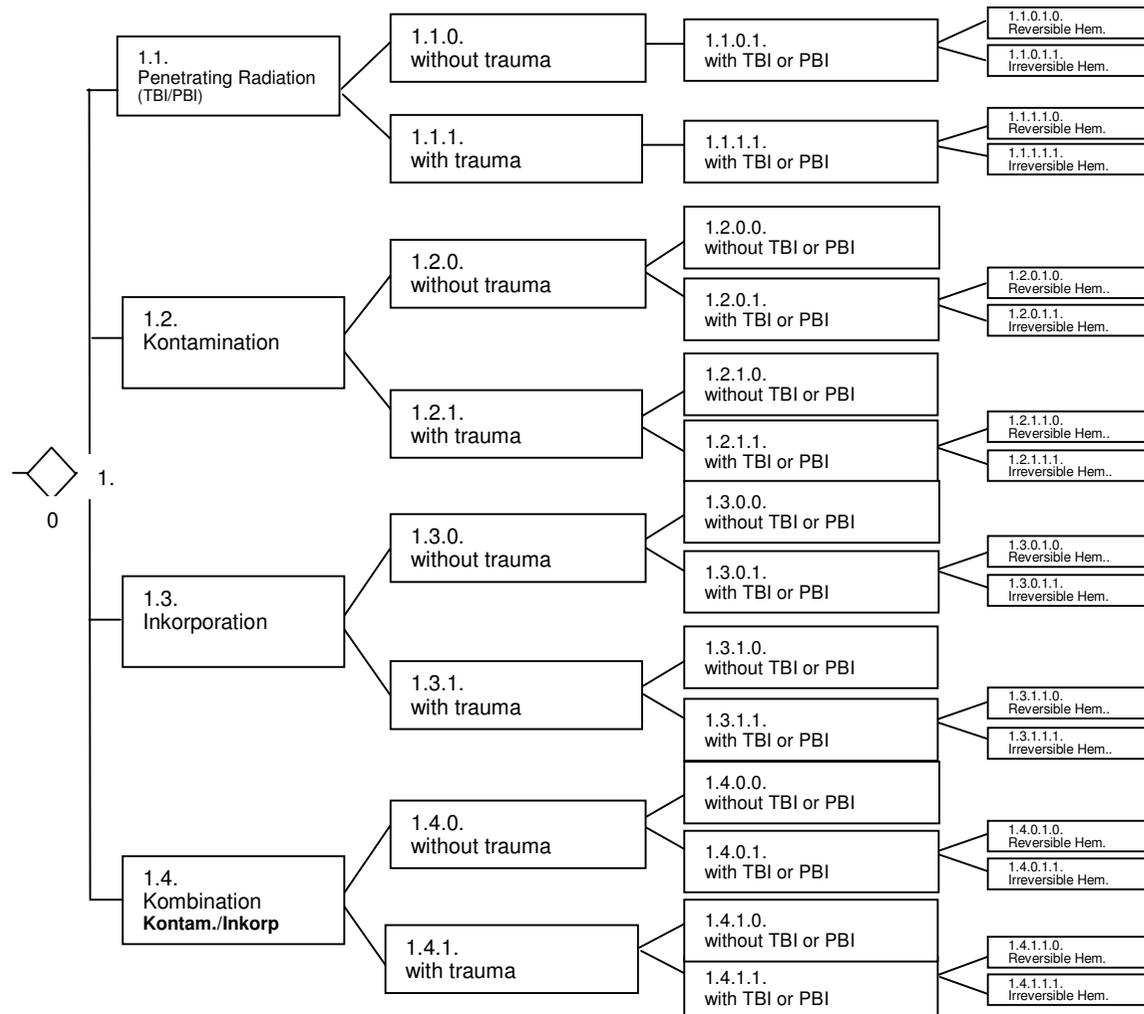
	Response-Category	General Therapeutic interventions	Institutional requirements
Complexity of clinical care ↑	RC 4 Autologous recovery most unlikely	Stem cell-transplantation	Specialised hospital with experience in all areas of intensive care medicine, particularly allogeneic SCT
	RC 3 Autologous recovery possible	Stimulation (growth factor therapy)	Internal haematological-oncological institutes with reverse isolation; Intensive care unit; Consultations of all medical specialities
	RC 2 Autologous recovery likely	Supportive care; Substitution (blood component therapy)	Medical wards with haematological, neurological and dermatological consultation services
	RC 1 Autologous recovery certain	General support of recovery processes; usually no specific therapy	Outpatient care or general medical wards

Requirements for the Radiation Accident Preparedness

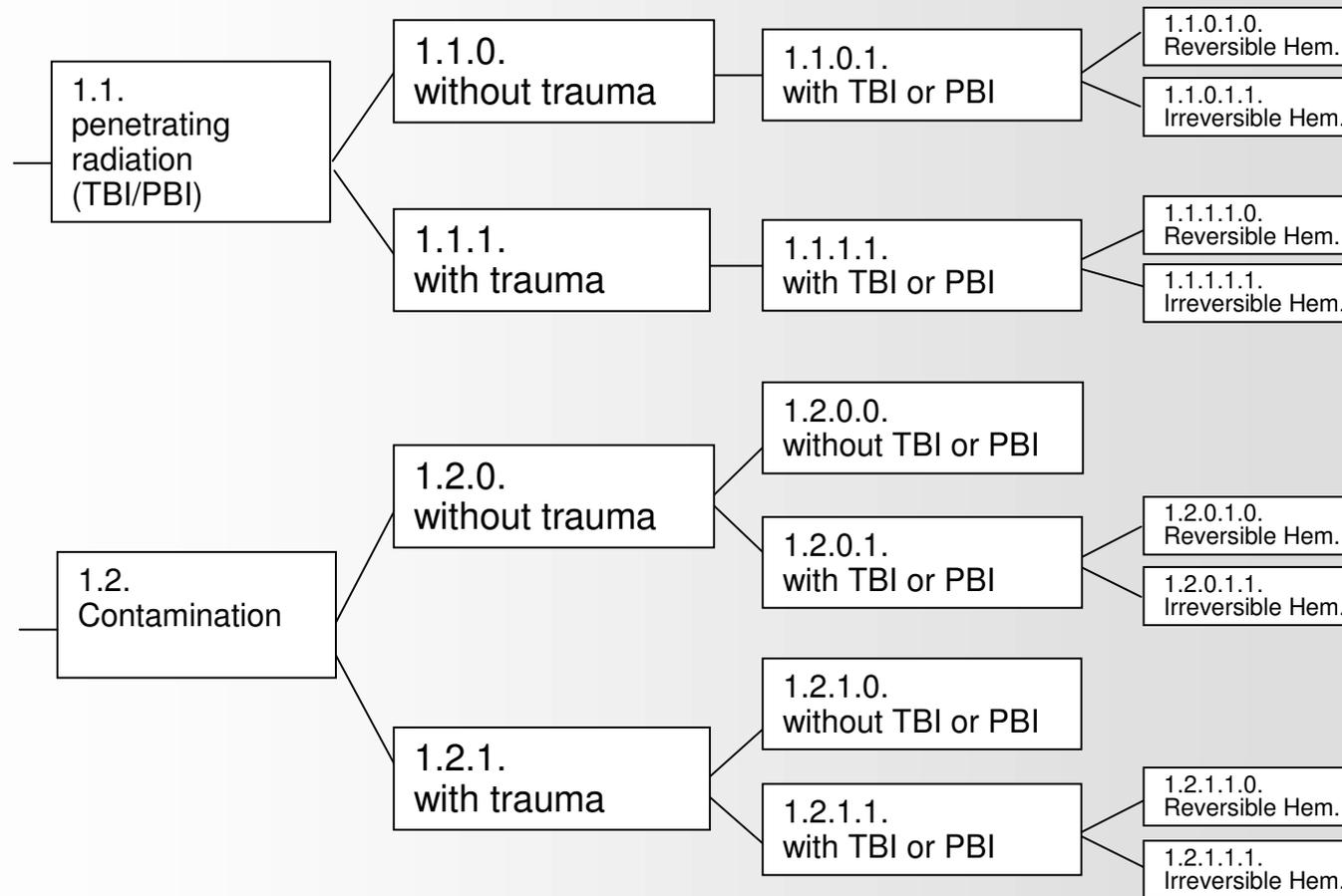
- ➔ Radiation Accidents: they may occur anytime and anywhere involving a few, many or hundreds or persons
- ➔ Problems to be addressed and solved beforehand:
Which patient should receive what diagnostic and therapeutic approaches and in what type of medical institution
- ➔ Development of:
 - distribution criteria (categories of patients according to type of accident)
 - admission criteria (is the hospital equipped to cope?)
 - Treatment criteria (is the hospital capable to provide best possible care?)

Categorization of Radiation Accident Victims in Order to Select Appropriate Management and Treatment Facilities

- 1. **digit:** exposed to IR:
0= No 1= Yes
- 2. **digit:** type of exposure :
1-4
- 3. **digit:** with trauma
0= No 1= Yes
- 4. **digit:** with TBI or PBI:
0= No 1= Yes
- 5. **digit:** irrevers. Hem.:
0= No 1= Yes



Categorization of Radiation Accident Victims Using Category 1.1 and 1.2 as Example



Radiation Accident Management: Admission Criteria Based on an Appropriate Code

Principle:

- Each patient will be assigned to one of the categories 1.1, 1.2, 1.3 or 1.4
- Based on additional injury and situation the patient will be characterized by a 5 digit code (from 1.1.0.1.0 to 1.4.1.1.1)
- Each digit has a logistic relevance

digit 1: radiation exposed	1 yes/ 0 no
digit 2: Type of exposure with the highest priority	1 or 2 or 3 or 4
digit 3: additional physical/ chemical/ thermal injury	1 yes/ 0 no
digit 4: TBI or PBI	1 yes/ 0 no
digit 5: Irreversible damage to hematopoiesis	1 yes/ 0 no

Conclusions

Cutaneous radiation syndrome as an independent prognostic factor of the acute radiation syndrome

Radiation combined Injuries has to be taken into account in radiation accident medical management (mass casualty scenarios / triage)

Concept of radiation-induced multi-organ-involvement and failure as a new basis for the understanding of radiation syndromes and as a focus of research in the pathophysiology of radiation syndromes and radiation combined injuries in search for therapeutic principals